Nonotogenic skull base osteomyelitis in children: two cases and a review of the literature

Trück, Johannes ; Thompson, Ameeka ; Dwivedi, Reena ; Segal, Shelley ; Anand, Geetha ; Kelly, Dominic F

Abstract: Skull base osteomyelitis is a rare condition in childhood and can be described according to whether it is associated with spread of infection from the middle ear (otogenic) or not (nonotogenic). Early recognition of this serious disease and prompt treatment are key to preventing extension to adjacent vascular and nervous system structures. Diagnosis can be challenging due to the variable presentation of the disease and potentially subtle radiological appearances. We present 2 cases of nonotogenic skull base osteomyelitis in childhood both affecting the clivus and review the 6 cases previously described. Both children presented with fever, headache and neck stiffness and responded well to medical management alone; detailed imaging was key to making a diagnosis.

DOI: https://doi.org/10.1097/INF.0000000000000782

activity and its consequence, such as unintended pregnancies and sexually transmitted diseases, when diagnosing *S. saprophyticus* UTIs in female teenagers.

REFERENCES

1. Pead L, Maskell R, Morris J. Staphylococcus saprophyticus as a urinary pathogen: a six year prospective survey. *Br Med J (Clin Res Ed)*. 1985;291:1157–1159.
2. Eriksson A, Giske CG, Ternhag A. The relative importance of Staphylococcus saprophyticus as a urinary tract pathogen: distribution of bacteria among urinary samples analysed during 1 year at a major Swedish laboratory. *APMIS*. 2013;121:72–78.
3. Schito GC, Naber KG, Botto H, et al. The ARESC study: an international survey on the antimicrobial resistance of pathogens involved in uncomplicated urinary tract infections. *Int J Antimicrob Agents*. 2009;34:407–413.
4. Wallmark G, Arremark I, Telander B. Staphylococcus saprophyticus: a frequent cause of acute urinary tract infection among female outpatients. *J Infect Dis*. 1978;138:791–797.
5. Lo DS, Shieh HH, Ragazzi SL, et al. Community-acquired urinary tract infection: age and gender-dependent etiology. *J Bras Nefrol*. 2013;35: 93–98.
6. Hayami H, Takahashi S, Ishikawa K, et al. Nationwide surveillance of bacterial pathogens from patients with acute uncomplicated cystitis conducted by the Japanese surveillance committee during 2009 and 2010: antimicrobial susceptibility of Escherichia coli and Staphylococcus saprophyticus. *J Infect Chemother*. 2013;19:393–403.
7. Sousa VS, Rabello RF, Dias RC, et al. Time-based distribution of Staphylococcus saprophyticus pulsed field gel-electrophoresis clusters in community-acquired urinary tract infections. *Mem Inst Oswaldo Cruz*. 2013;108:73–76.
8. Vincent CR, Thomas TL, Reyes L, et al. Symptoms and risk factors associated with first urinary tract infection in college age women: a prospective cohort study. *J Urol*. 2013;189:904–910.
9. Oliveira-Campos M, Giatti L, Malta D, et al. Contextual factors associated with sexual behavior among Brazilian adolescents. *Ann Epidemiol*. 2013;23:629–635.
10. Ministério da Saúde. Proporção de nascidos vivos de mães adolescentes [DATASUS webside]. 2012. Available at: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?idb2012/g15.def. Acessed February 11, 2015.
11. Hedman P, Ringertz O. Urinary tract infections caused by Staphylococcus saprophyticus. A matched case control study. *J Infect*. 1991;23:145–153.
12. Hovelius B, Mårdh PA. Staphylococcus saprophyticus as a common cause of urinary tract infections. *Rev Infect Dis*. 1984;6:328–337.

NONOTOGENIC SKULL BASE OSTEOMYELITIS IN CHILDREN

TWO CASES AND A REVIEW OF THE LITERATURE

Johannes Trück, MD, DPhil, Ameeka Thompson, BMBCh,* Reena Dwivedi, MBBS, MRCS, FRCR,† Shelley Segal, MRCPCH, PhD,* Geetha Anand, MRCPCH,‡ and Dominic F. Kelly, MRCPCH, PhD**

Abstract: Skull base osteomyelitis is a rare condition in childhood and can be described according to whether it is associated with spread of infection from the middle ear (otogenic) or not (nonotogenic). Early recognition of this serious disease and prompt treatment are key to preventing extension to adjacent vascular and nervous system structures. Diagnosis can be challenging due to the variable presentation of the disease and potentially subtle radiological appearances. We present 2 cases of nonotogenic skull base osteomyelitis in childhood both affecting the clivus and review the 6 cases previously described. Both children presented with fever, headache and neck stiffness and responded well to medical management alone; detailed imaging was key to making a diagnosis.

Key Words: child, clivus, fever, infection, headache, neck pain, osteomyelitis, skull base

Accepted for publication March 2, 2015.

From the *Paediatric Infectious Diseases and Immunology, University Department of Paediatrics, Oxford, United Kingdom; †Department of Neuroradiology, and ‡Department of Paediatrics, John Radcliffe Hospital, Oxford, United Kingdom.

Drs. Trück and Thompson acquired patient data, drafted the initial manuscript; Drs. Dwivedi, Segal, Anand and Kelly reviewed the manuscript and made substantial additions to the manuscript; all authors approved the final manuscript as submitted.

The authors have no funding or conflicts of interest to disclose.

Author for correspondence: Johannes Trück, MD, DPhil, Paediatric Infectious Diseases and Immunology, University Department of Paediatrics, Level 2, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom. E-mail:johannes.truck@paediatrics.ox.ac.uk.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

DOI: 10.1097/INF.0000000000000782

Skull base osteomyelitis (SBO) is a rare condition most typically associated with malignant otitis externa in adults (otogenic) with underlying diabetes mellitus or some form of immunosuppression.[1] Less frequently, cases of nonotogenic SBO have also been described[2] where there is no concurrent otitis and in which infection may arise from the paranasal sinuses, the retropharynx, hematogenous spread or represent a recrudescence of partially treated malignant otitis externa.[2] Both conditions are rare in childhood with only 6 cases of nonotogenic SBO previously described and most of these in children without comorbidities. We describe a further 2 cases of nonotogenic SBO in immunocompetent and previously healthy children, both of who had a good outcome with conservative medical management. These cases add to the current literature and emphasize the importance of detailed imaging and interpretation from experienced radiologists to ensure early diagnosis and facilitate prompt investigation and treatment.

CASE ONE

An 11-year-old girl presented to our emergency department with a 7-day history of fever and a 4-day history of generalized neck pain exacerbated by movement. Other symptoms included right-sided otalgia and intermittent headache. There was no history of foreign travel and no relevant past medical history. Physical examination including neurological assessment was unremarkable apart from pain on lateral flexion and extension of the neck. She was afebrile with normal observations, and the blood tests showed raised C-reactive protein (CRP > 156 mg/L) and mild neutrophilia (7.8×10^9/L). A lumbar puncture performed at admission was normal with 2 white blood cells/μL (all lymphocytes), normal protein and glucose. Intravenous broad-spectrum antibiotics (ceftriaxone) were started and on the next day fibronasoendoscopy, ultrasound of the neck, and magnetic resonance imaging (MRI) of the cervical spine were undertaken all of which were reported as normal. Over the following 24 hours, her symptoms progressed with further restriction of neck movement resulting in computed tomography (CT) of the head and neck which demonstrated no abnormalities. A blood culture taken before starting antibiotics grew a fully sensitive *Streptococcus intermedius* (*Streptotoccus milleri* group), and oral clindamycin was added. On day 4, ongoing symptoms prompted re-review of the original MRI on which a skull base lesion was then suggested (see Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C179). Subsequently, the patient underwent whole-body bone scan in addition to SPECT/CT of the skull base to C4. This showed abnormally increased tracer

uptake within the clivus, centered on the growth plate, consistent with osteomyelitis of the clivus and a small subperiostal abscess (see Fig., Supplemental Digital Content 1, http://links.lww.com/INF/C179). Marked clinical improvement in pain and neck mobility was noted from day 5 and subsequently she was able to receive ambulatory care. A 6-week course of IV ceftriaxone and oral clindamycin followed by 6 weeks of oral co-amoxiclav resulted in complete resolution of the symptoms and an MRI performed almost 3 months after disease onset showed substantial improvement in marrow signal of the clivus with no features of edema and a reduction in volume of the subperiostal abscess. There has been no recurrence over a follow-up period of 1.5 years.

CASE TWO

An 11-year-old boy of Asian origin with no relevant past medical history and no history of foreign travel presented to our emergency department with a 3-week history of fever, neck pain, neck stiffness and headache together with a dry cough for 1 week. The neck pain was exacerbated by movement. On examination, he was febrile (38.4°C) and had a limited range of movement of his neck in all directions due to pain but physical examination including detailed neurological assessment was otherwise unremarkable. The blood test results showed a CRP of 52 mg/L, mild neutrophilia (10.0×10^9/L) and normal chest X-ray. He was started on intravenous ceftriaxone while further radiological investigations were arranged. An initial MRI had to be abandoned due to distress of the patient and a further attempt on day 2 showed a lesion in the clivus. For further characterization, a gadolinium-enhanced MRI in conjunction with a CT was performed on day 3 demonstrating a lesion extending anteriorly from the clivus into the preclival soft tissue (see Fig., Supplemental Digital Content 2, http://links.lww.com/INF/C180). This was of high signal on T2w and STIR imaging, low signal on T1w imaging and demonstrated peripheral contrast enhancement with central diffusion restriction consistent with hyper-cellular content (see Fig., Supplemental Digital Content 2, http://links.lww.com/INF/C180). Imaging appearances were consistent with an abscess. The CT highlighted focal erosion of the cortex of the clivus anteriorly (see Fig., Supplemental Digital Content 2, http://links.lww.com/INF/C180). It was felt that neurosurgical intervention was not necessary at this stage and so the patient was treated conservatively with intravenous antibiotics for 6 weeks followed by 6 weeks of oral clindamycin. The blood culture taken before starting antibiotics remained negative. An MRI scan after 4 weeks of treatment showed improvement of the abscess but not full resolution. On completion of antibiotic treatment, the patient was asymptomatic. There has been no recurrence over a follow-up period of 1 year.

As part of the initial work-up, the patient underwent screening for tuberculosis (TB) and showed positive results for both the tuberculin skin test and an interferon-gamma release assay consistent with previous exposure to *Mycobacterium tuberculosis*. Given the clinical improvement on conventional antibiotics TB disease as a cause of the SBO was considered unlikely and chemoprophylaxis to treat TB infection was given after completion of treatment for SBO.

DISCUSSION

SBO has the potential to cause major sequelae through the proximity within the neck of important vascular and neurological structures. It is a rare diagnosis in childhood and therefore may not be considered early on in the context of the more common presenting features of neck pain and fever. Prior to the cases in this report, there are 6 previous reported cases of nonotogenic SBO[3–8] which are summarized in Table 1. Based on the published cases along with our cases it appears that the most consistent clinical features associated with this pathology are fever, neck pain and stiffness and occasionally cranial nerve palsy. These clinical signs and symptoms are nonspecific and may also been seen in other pathologies affecting

TABLE 1. Details of Previously Reported Nonotogenic Skull Base Osteomyelitis Cases in Children

Age, Sex, Diagnosis	Comorbidities	Symptoms	Neurological Signs	Surgical Management	Microbiology (M) and Antibiotics (A)	References
<17 years, Facial cellulitis, SBO + abscess	-	?	?	Incision and drainage	M: *Streptococcus milleri, Eikenella corrodens* A: ?	3
13 years, M, SBO	Diabetes mellitus	Fever, headache	Cranial nerve palsy	Sphenoidotomy	M: *Staphyloccocus aureus, Serratia marcescens, Aspergillus niger* (all from pus) A: 6 weeks broad-spectrum antibiotics	4
5 years, F, Sella turcica abscess + sinusitis	-	URTI, headache, anorexia, vomiting, lethargy	6th nerve palsy	-	M: ? A: Cefotaxime	5
6 years, F, Clivus abscess	-	Fever, neck pain and stiffness; photophobia, headache	-	Incision and drainage	M: *Enterococcus faecium* (from pus) A: 18 days IV antibiotics (cefotaxime/gentamicin/teicoplanin/vancomycin/metronidazole), 3 months oral ciprofloxacin	6
3 years, F, Clivus abscess	-	Fever, neck pain, cervical lymphadenopathy	-	Image-guided aspiration + endocopic drainage	M: Peptostreptococcus (from pus) A: 4 weeks IV Meropenem, 2 weeks oral Co-amoxiclav	8
10 years, F, Sinusitis + SBO	Chronic sinusitis, ASD repair	Fever, neck stiffness	Facial palsy, ptosis, dysarthria, encephalopathy	Inferior meatus antrostomy and right maxillary sinus washout	M: *Streptotoccus milleri* (pus from maxillary sinus) A: 2 months IV cefotaxime + metronizole	9

ear, neck and throat areas, such as retropharyngeal abscess,[9,10] Lemierre's syndrome[11] or meningitis.[12]

Because of the nonspecific nature of clinical signs with SBO a high index of suspicion should be maintained for patients with a combination of fever, headache, neck pain or torticollis with or without cranial nerve palsy and in whom no obvious focus can be established. It is quite possible that due to the nonspecific signs and symptoms, highlighted by the 2 cases described in this report, nonotogenic SBO may be more frequent than previously reported in the literature. Imaging modalities that have a role in the investigation of suspected SBO include MRI, CT and bone scan with or without SPECT/CT. MRI has the highest sensitivity and specificity for the diagnosis of osteomyelitis and it has better soft tissue discrimination than CT.[13] MRI is safe as there is no radiation risk but the prolonged imaging time compared with CT means that some children require general anesthesia before it can be carried out. This was necessary for case 2, and led to a delay in image acquisition and establishing of the diagnosis. Changes seen on MRI and CT can be subtle as demonstrated by our first case, where both MRI and CT were initially reported as normal. When this is the case but there is high clinical suspicion of SBO, a SPECT/CT could prove useful, which may also help to further improve exact anatomical localization.[14,15]

In some patients, management may involve surgery to drain collections if identified and to obtain a microbiological diagnosis although the need for surgical intervention needs to be discussed on a patient-by-patient basis. Five out of 6 of the cases previously described underwent surgery in the setting of progressive neurological signs. In our cases, there was no neurological involvement and marked improvement of symptoms occurred within a small number of days with conservative therapy only. A wide variety of Gram-positive and Gram-negative bacteria have been isolated previously for nonotogenic disease in adults and children with *Pseudomonas sp.* dominating published adult cases[2] whereas in children the microbiology seems to be more variable (Table 1). In cases in which SBO is suspected, it may therefore be prudent to use antibiotic agents with good bone penetration, which cover both Gram-negative and Gram-positive bacteria.

Classically, SBO has been described as a complication of otitis externa, which seems to be more common in older diabetic patients, usually caused by *Pseudomonas aeruginosa*.[2] Less commonly, SBO can be nonotogenic, often affecting the sphenoid and occipital bones, especially the clivus[2] and in some cases it may represent a complication of sinusitis.[16] Some organisms associated with nonotogenic SBO form part of the normal oral flora and it seems therefore possible that nonotogenic SBO is the result of first sinus disease, which then spreads continuously to the base of the skull. However, only case 2 described in this report showed radiological signs consistent with maxillary sinusitis and opacification of the ethmoid cells whereas paranasal sinuses were patent in case 1 suggesting a different route of infection in this patient.

There are no definitive guidelines for the treatment of SBO in children, given its rarity and a consequent lack of clinical studies. Both of our cases were treated with intravenous antibiotics for 6 weeks, followed by 6 weeks of oral antibiotics. Both cases responded well to medical management negating the need for surgical treatment. Previous cases reported in the literature vary so greatly in terms of presentation, severity and etiology that it is hard to draw any conclusions from them regarding the best mode and duration of treatment other than that the clinician should be guided by the individual patient.

REFERENCES

1. Adams A, Offiah C. Central skull base osteomyelitis as a complication of necrotizing otitis externa: imaging findings, complications, and challenges of diagnosis. *Clin Radiol*. 2012;67:e7–e16.
2. Clark MP, Pretorius PM, Byren I, et al. Central or atypical skull base osteomyelitis: diagnosis and treatment. *Skull Base*. 2009;19:247–254.
3. Han JK, Kerschner JE. Streptococcus milleri: an organism for head and neck infections and abscess. *Arch Otolaryngol Head Neck Surg*. 2001;127:650–654.
4. Chang PC, Fischbein NJ, Holliday RA. Central skull base osteomyelitis in patients without otitis externa: imaging findings. *AJNR Am J Neuroradiol*. 2003;24:1310–1316.
5. Taranath A, Prelog K. Sella turcica collection due to skull base osteomyelitis. *Pediatr Radiol*. 2005;35:451.
6. Rusconi R, Bergamaschi S, Cazzavillan A, et al. Clivus osteomyelitis secondary to Enterococcus faecium infection in a 6-year-old girl. *Int J Pediatr Otorhinolaryngol*. 2005;69:1265–1268.
7. Bates DD, Shetty AK, Kirse DJ. Treatment of a clivus abscess in a child using image-guidance. *Int J Pediatr Otorhinolaryngol Extra*. 2006;1:207–212
8. Ng J, Connolly DJ, Rittey CD, et al. Skull base osteomyelitis leading to lateral medullary syndrome in a child. *Eur J Paediatr Neurol*. 2007;11:111–114.
9. Page NC, Bauer EM, Lieu JE. Clinical features and treatment of retropharyngeal abscess in children. *Otolaryngol Head Neck Surg*. 2008;138:300–306.
10. Grisaru-Soen G, Komisar O, Aizenstein O, et al. Retropharyngeal and parapharyngeal abscess in children–epidemiology, clinical features and treatment. *Int J Pediatr Otorhinolaryngol*. 2010;74:1016–1020.
11. Karkos PD, Asrani S, Karkos CD, et al. Lemierre's syndrome: a systematic review. *Laryngoscope*. 2009;119:1552–1559.
12. Visintin C, Mugglestone MA, Fields EJ, et al. Management of bacterial meningitis and meningococcal septicaemia in children and young people: summary of NICE guidance. *BMJ*. 2010;340: C3209.
13. Faust SN, Clark J, Pallett A, et al. Managing bone and joint infection in children. *Arch Dis Child*. 2012;97:545–553.
14. van der Bruggen W, Bleeker-Rovers CP, Boerman OC, et al. PET and SPECT in osteomyelitis and prosthetic bone and joint infections: a systematic review. *Semin Nucl Med*. 2010;40:3–15.
15. Bolouri C, Merwald M, Huellner MW, et al. Performance of orthopantomography, planar scintigraphy, CT alone and SPECT/CT in patients with suspected osteomyelitis of the jaw. *Eur J Nucl Med Mol Imaging*. 2013;40:411–417.
16. Laurens MB, Becker RM, Johnson JK, et al. MRSA with progression from otitis media and sphenoid sinusitis to clival osteomyelitis, pachymeningitis and abducens nerve palsy in an immunocompetent 10-year-old patient. *Int J Pediatr Otorhinolaryngol*. 2008;72:945–951.

OPEN

FAILURE OF A SINGLE VARICELLA VACCINATION TO PROTECT CHILDREN WITH CANCER FROM LIFE-THREATENING BREAKTHROUGH VARICELLA

James Kelley, MD, JD, Debra Tristram, MD,* Masaki Yamada, MD,† and Charles Grose, MD†*

Abstract: We report 2 children with life-threatening breakthrough varicella. Both had received 1 varicella vaccination before onset of cancer. Despite treatment with intravenous acyclovir, 1 child died of disseminated varicella. Because similar fatal cases have been reported, high-risk immunocompromised children with 1 varicella vaccination may warrant the same varicella prophylaxis as immunocompromised children who have never been vaccinated.

Key Words: varicella vaccine, varicella deaths, acyclovir

Accepted for publication March 23, 2015.

From the *Division of Pediatric Infectious Diseases, Albany Medical College, Albany New York; and †*Division of Infectious Diseases/Virology, Children's Hospital, University of Iowa, Iowa City, Iowa.*

The authors have no funding or conflicts of interest to disclose.

Address for correspondence: James Kelley, MD, PhD, Department of Family Practice, Hershey Medical Center, 500 University Drive, Hershey PA 17033. E-mail: kelleyjemail@gmail.com.

DOI: 10.1097/INF.0000000000000737